Hallucinogens: Neurochemical, Behavioral, and Clinical Perspectives, edited by B. L. Jacobs.
Raven Press, New York © 1984

LSD: The Bridge from Human to Animal

Daniel X. Freedman

Department of Psychiatry, University of Chicago, Chicago, Illinois 60637

Having personally paced the bridge from human to animal for almost 30 years, and often finding ultimate explanatory destinations as a mirage—intensely visible, salient to the moment's needs, but aggravatingly elusive to grasp—I hesitate to expose an unseemly reach. While a view from the bridge calls for perspective, too often one has the sense of suturing fleeting clouds. If one focuses solely on the striking array of effects of lysergic acid diethylamide (LSD) and related psychoactive indoles and phenylethylamines, a number of different explanatory syntheses have been attempted. These start with different observations—experiential, clinical, anthropologic, ethologic, biochemical, behavioral, neurophysiologic—and often with different purposes in mind. These drugs, then, generate inquiry across a range of phenomena in which biobehavioral correlates of the fact or structure of human subjective experience might be at issue.

Some seek to illumine the nature of mind and mysticism, to gain insight into (or access to) creativity or new learning, or a new therapeutics; others aim to understand the schizophrenias, or to find the clue to an endogenous psychotoxin unique to these disorders; and more commonly there are those who would discover etiologic or (preferably) mediating neurobehavioral and biologic mechanisms which might or might not be directly relevant to events in the clinic or meditative retreat. While others see an opportunity to study the psychobiology of perceptual mechanisms, many seem, often simplistically, to search for a unitary cause of hallucinations. Still others focus on "the meaning of amines" or a possible compellingly psychotomimetic configuration at the molecular or submolecular level. In this melange of purpose—observation, sporadic or systematic experiment, anecdote, and inference—it is not surprising that adjudicated fact, careful assessment of evidence, and systematic search for the contradictory (let alone the confirmatory) are too often missing, in either conclusory assertions, ascriptive discourse, or ad hoc assumptions underlying various experimental approaches.

What is encouraging for keeping watch on the bridge is the renewed pace, relevance, and even rigor with which components of the effects of LSD are being pursued in a range of research paradigms. If the bridge from human to animal is stipulated in the framework of biobehavioral sciences, the obvious

purpose is to understand how it is that human behavior and experience can occur as it does (requiring its accurate description, analysis, and test), and to discover mechanisms, processes, or leads in animals that might be tested to that end in man. It is in one sense a preposterous query, clearly one that ultimately awaits discoveries in neurobiology and human psychology by which brain operations and their parameters can be soundly linked to physiologic and behavioral processes. A part of the grand agenda of the life sciences is to find the essential element or parameter of an adaptive sequence or behavioral variable (whether dependent or independent) for which neuronal operations might be relevant. Thus molecular biology would hope to move from gene to phenotypic expression and appreciate the multiple complex paths to a phenotype. Nor, in retrospect, would there be apologies that, in the search for designs by which organizations are achieved and evolve, such banal witnesses as garden peas, fruit flies, yeast, bacteria, and fossils provided a bridge.

On this bridge, we need not apologize for assuming that biophysical and biochemical events reflect not only cellular changes but changes in the integration and control of small or large components of an organ, the function of which creates the links of the behaving mind and body. One would have to suppose that, at bottom, this is what actuates our interest, whether we work with snails or humans. Clearly, in neurobiology, aspects of sensitization and habituation (and perhaps of learning)—in terms of the effect of a signal on membrane processes and temporal interactions with ongoing action potentials—are now elegantly discerned (44). In both animals and humans, mnemonic, motivational, and affective components of subjectively vivid or strange experience (and behavior) apparently require limbic brain function as a substrate (38). Different roughly defined classes of psychotropic drugs differentially affect transmission, transmitters, and receptors. While detailed charts are few, there are occasional landmarks. Simply making a journey can expose new rules of the road and new territory. Elegance in linking a sequence of mechanism and actions to effect is rare, from whichever end of the bridge one takes his vantage. Yet there is reason to believe that persistent research into the mode of action of hallucinogenic drugs can lead to dissections and discoveries congruent with the grand design.

Whether we look at biopsychology, neurobiology, or psychiatry, different paths of inquiry and their languages are difficult to integrate and to keep conceptually clear. This is intrinsically difficult. We know we are dealing with an ongoing system and, in a sense, with five brains: neuroanatomic, electrophysiologic, monoaminergic, and peptidergic—if not ionic and molecular—and neurobehavioral. Thus, having reviewed aspects of LSD at least a dozen times since 1965 (3,23,25–28,30–34,36), I could regrettably create a catalog of carelessness (my own and others), dangling findings awaiting new knowledge before significance can be gained, observations uncoupled to function, or simply mislabeled as to process or mechanism, and hence missed opportunities for systematic investigation in both human and animal research.

Even in the simplistic sense, disturbed perceptual mechanisms, illusions, and

hallucinatory vividness are not a clinical diagnosis, occur via many routes and contexts, and, along with the deployment of attention, arousal, thought, and affective processes, comprise a part of the picture of mental function. No more than an antihistamine can be thought of as solely antihistaminic, can we be trapped by labels—ascriptions of convenience—whether we speak of amine blockers or "hallucinogens," the psychotomimetics, psychedelics, or mysticomimetics. Every drug has patterns of action and effect that will differ in minor or major ways from congeners, and these complexities need not distract one if operational precision is kept in mind.

To improve traffic, let alone firm the bridge's bipolar anchors, we all, I suppose, could strive for precision, providing operational referents, whether speaking of human experience or the range of particular receptors linked to particular processes (and organisms, from cockroach to goats and humans) under current study. Thus I briefly review the basis of some of my own observations, then some essentials of the experience with the drug in humans useful for biologic and animal investigations, and, finally, some overall tactics or approaches that might be useful at each end of the bridge.

BRIEF RETROSPECT

In investigating LSD or hallucinogens, it would be useful to keep in focus what feature of pharmacologic or neurobehavioral interest is being sought. One could simply want to know about a drug—its pharmacodynamics, sites of action, and array of effects. One could also use a drug to know about something—a tool to investigate biologic systems, a probe to elicit fundamental regulatory mechanisms in cells and cellular systems, and in human or rat investigations to determine what aspects of a dysfunction are repaired or aspects of normal function are dissociated or altered (which in turn leads to a new perspective on the capacity of the organism and questions of underlying mechanisms). Both have, in fact, been done.

This is noted since the intense flurry of studies of LSD in humans had occurred between 1947 and 1957, at a time when biochemistry of the major psychoses offered no lead that could rationally command pursuit, and central nervous system (CNS) pharmacology was rudimentary. The presence of acetylcholine, norepinephrine (NE), and serotonin (5-HT) in brain came to be known within that decade, but not their localization, link to cellular organizations, or function. The useful effects of reserpine in schizophrenia had most strikingly stipulated a link of brain amines and behavior only when concomitant sedative and 5-HT-releasing effects were later discovered in 1955. By 1957, monoamine oxidase inhibitors (MAOIs) as "psychic energizers" were linked to an elevation of brain amines and their possible utility as antidepressants. Exciting knowledge of how the brain, operating as more than a switchboard, might produce graded states of consciousness and intensity in affective and cognitive function, derived from discoveries including the ascending and descending reticular systems. There

were also demonstrations through ablation and implanted depth electrodes of the role of subcortical and limbic systems in pleasure and pain, and appetitive, sexual, and aggressive dimensions of behavior. While mescaline had been noted to be structurally linked to NE, the search for biotransformations into putative endogenous psychotogens (adrenochrome) was fruitless. For the wrong reasons, the right investigations into the enzymatic mechanisms regulating synthesis and catabolism (and, later, nerve ending mechanisms regulating catecholaminergic function) were indeed stimulated, and advances in fundamental knowledge, led by Axelrod and others, ensued.

For LSD, by 1957 some of the essential behavioral effects in humans had been roughly delineated in clinical reports and systematic human psychopharmacologic studies largely pursued by Abramson and Jarvik, Kornetsky, and Isbell (26,60). Taken together, one could extract from these reports a rough map of the basic phenomena in man, although gropings with such strange phenomena as initially observed in unsystematic clinical studies led to an expectably florid range of assertion and inference. Nor have we entirely escaped their residue in either animal or human study as, in the 1970s and 1980s, human investigations especially have lagged. This, in part, is because of a major lack of systematic questions (pharmacologic, psychopathologic, and psychophysiologic), in part because of an ascendancy of "fringe" as well as therapeutic interests difficult to put into designed research, and in part because of the difficult social problems in conducting orderly, safe, and sober inquiry. Between 1957 and 1968, the major emphasis in human investigation sharply tapered off to a few systematic studies of therapeutic efficacy of different uses of LSD. These were eventually largely suspended as the abuse of LSD and psychiatric consequences of lay experimentation became a subject matter in their own right.

In 1957, then, at one end of the bridge were mollusks, uterine fundi, liver fluke, and gut, from which classic pharmacology could deduce drug action and receptor linked function, and at the other, an array of clinical puzzles, of dissociated behaviors, and a pattern of effects (in humans, spiders, fish, and important structure-activity relationships of ergots in rabbit) that had yet to be linked to any biochemically mediated process in brain. Animal experimentation had shown dehabituation (the familiar becomes novel), and fundamentally that the drug facilitated reactivity of reticular systems to environmental input. Differential changes in optic and auditory pathways were deduced from animal experiments, low dose LSD enhancing certain sensory systems and simultaneously inhibiting the responsiveness of various cortical systems and inhibitory effects of LSD and 5-HT on human and animal cortical cells. The general picture was of a behavioral state in which there was enhanced input with diminished and more variable control. The structural similarities of LSD and 5-HT, while physiologically borne out in *in vitro* studies, had yielded no link in brain, and the lack of psychotomimetic effect of the potently anti-5-HT LSD congener 2-brom-LSD (BOL) (and other ergot congeners) was widely taken as an indication that there was none.

My bias, then, reinforced by gifted students, was that the potency and reliability of LSD were too unique to ignore, and that both ends of the bridge required some systematic focus for useful traffic. Furthermore, it did not seem that genetic or biochemical change—if these actually existed in clinical disorder—produce a diagnosis, but rather shifts in neuronal systems, such that the range of signals and thresholds for different components of interlinked brain operations (and hence behavioral dimensions and effects) would be altered. Thus the use of LSD as a "model" was selected not because of any evident immediate or future clinical relevance, but rather because the drug reliably created periods of neurochemical and physiologic change—a chemically determined package of time (23)—during which sequences of subjective effects unfolded. Components of these effects could be readily observed in a range of acute psychotic and prepsychotic states, and in the case of LSD, a chemical trigger to events was undeniable. For both the brain biochemical and behavioral effects, LSD should provide a reliable way of tracing a sequence of effects and mechanisms and sites for them. A systematic study should yield evidence of mechanisms that could occur in nature, and expanded knowledge of brain function might be a useful spin-off. There were admittedly idiosyncratic motives as well—one beyond querying the dominant thesis of the day—that psychopathology was solely explained by learning. Having focused on CNS mechanisms in psychosis and allergy and the central actions of antihistamines, I had an illogical and certainly a hubristic hope that "tolerance" could be usefully investigated. Clinical work with families at high risk for schizophrenia, and offspring who did not develop the disorder, made any mechanism by which a psychotogen could "turn itself off" attractive to pursue.

Mechanisms of tolerance (for both morphine and LSD) remain elusive, but it was perhaps a fortunate beginning with respect to subsequent findings. Tolerance is a decrement of effect contingent on dosage schedule, and its analysis requires sorting out an array of reliable physiologic and behavioral effects and careful attention to temporal parameters. Thus with the general notion of studying periods of drug-induced biochemical changes and concomitant sequences of behavioral changes, we began a series of studies at Yale which branched off to a variety of systematic inquiries. Beginning with rewarded rope climbing behavior and later fixed ratio schedules of reinforcement in the rat, time parameters for the sequence of aminergic events, neurophysiologic changes, drug pharmacodynamics, behavioral effects, and characteristics of tolerance and cross tolerance were investigated. While commencing rat behavioral projects (19,20), I was able to systematically study both tolerance and acute tolerance in volunteer subjects at the National Institute of Mental Health (NIMH). More important, with various dosage schedules repeated in the same set of collaborative informers (prior to the period of frenetic psychedelic expectancies), one could remap the essential sequence of effects over a 10-month period and appreciate the environmental and personality sources of variability as well. Thus it was possible to test the regularity of the sequence of probable states in both schizophrenic

(21,26) and postdelirium tremens volunteers in observing the peyote ceremonial and, later, respectively, in studies of the aftereffects in lay experimenters (12,26,54).

When periods of acute behavioral change in rats were precisely coupled with brain biochemical measures, it was possible, by 1960, to establish a direct, stereospecific effect of LSD and psychoactive congeners on brain 5-HT levels (21a). The LSD effect was originally characterized as enhancing the binding of newly formed 5-HT to intracellular storage sites, and without direct effects on 5-HT enzymes. Fixed ratio schedules in rat met the criteria for a threshold dose and for tolerance and cross tolerance, with similar time parameters as in man. By 1963, it appeared to be simple (22): LSD and psychoactive congeners produced a unique pattern of small elevations of 5-HT and decrease in NE during a period of change in an array of electroencephalographic (EEG) (23), autonomic, and behavioral effects; furthermore, nonpharmacologic "stress" produced a similar pattern (6,22). Both an environmental and molecular signal appeared to converge in a common pattern of CNS aminergic response. The mechanisms for these changes are now, of course, differentiated. Nevertheless, changes in amine binding and release seemed to be related to a factor of intensity in both human and animal behavior, the amines appearing to modulate ongoing neurobehavioral regulations (23). The mirage of some unity in brain-mediated response to stress and molecules did spur further brain biochemical, behavioral, and electrophysiologic studies differentiating key processes. Unfortunately, this promising yield left time for only a terse report to the NIMH on human acute tolerance studies; and by 1966 (when I moved to Chicago), the feasibility of managing focused human investigations accountably and responsibly was minimal.

This is not the place to document what students, colleagues, and collaborators of that decade, as well as many others, have independently assembled and learned. Looking back, one sees striking advances in neuroanatomy and physiology in the ability to deduce important receptor or aminergic functions from behavioral analyses (67), a far better grasp of the link of aminergic function to component behavioral effects, a focus both on perikaryal and nerve ending events, and, while lagging, postsynaptic events as well. In the mid-1960s, Aghajanian and I (3) noted the recurrent difficulty of estimating the significance of biochemical findings viewed in isolation from the cellular systems that link chemical events to physiologic and behavioral effects. It is now clear, however, that the logic of how the CNS is built from dorsal root to cortex, and the arrangement of aminergic source cells at the raphe pacemaker and at cortical nerve endings that can facilitate or inhibit major afferent input, as well as the different 5-HT-LSD binding sites (and new systems of behavioral analysis relevant to them), can provide the text for future biobehavioral research. The focus on LSD has had utility. With general advances in biopsychology, one can no longer assume that arrays of known behaviors are started or stopped by an amine; rather, we can appreciate the interacting influences on any component system,

depending in part on the prior state of one or another significant variable. For LSD, the logic of coupling sequences of behavioral change and periods of biochemical and neurophysiologic change is evident and nicely demonstrated in the recent combined electrophysiologic, behavioral, and biochemical studies of LSD and tolerance in the freely moving cat (64). Thus we can turn to the question of what observations in man may require of and suggest for animal investigations and, occasionally, vice versa.

RELEVANT PARAMETERS OF LSD EFFECTS IN HUMANS

Without doubt, LSD compelled attention because of its stereospecificity, high potency, and reliability in producing a time-limited period of uniquely altered psychedelic mental functioning, as well as the striking structural and physiologic links to 5-HT systems. Less than one-billionth of a gram per gram of brain will signal a sequence: a march or train of multiple effects. While variably embellished, these effects are reliable in terms of basic periods of altered perceptual, affective, and mental functioning. However we describe the pattern and characteristics of the "trip," the enhanced clarity of consciousness in the presence of the diminished importance of reality, we must contrast the reliability of a single dose of LSD (and far less potent related drugs) with the amnestic and confusional effects of the cholinolytic deliriants and the dissociative anesthetics with neurologic and neurosensory effects. All these drugs differ from the uncertain psychotomimetic effects of single doses of amphetamine (especially in naive subjects) and the variability of mental response produced by enzyme inhibitors and amine precursors.

Onset and Offset of Effects

First we note that a threshold dose is necessary for the psychedelic sequence to be triggered; a dose of between 25 and 50 μg by mouth or intravenously is necessary. We lack systematic observations of subthreshold dosages. What is striking is that once begun, the trip unfolds through an acute phase (about 4 hr in man) and a 4- to 6-hr second phase. During the second 6 hr, the "TV show in the head" no longer compels interest; subjects think often that the effect is over but fairly regularly report (at, perhaps, 10 hr after an initial dose) that they had been at the least self-centered, and usually suspicious, with ideas of reference or even paranoid convictions. This LSD effect continues to go unstudied and unnoted in discourse on, or research design for, psychotomimetic and hallucinogenic studies.

With an increase in dosage, the total duration of effect is some minutes longer, but what is most marked is an increased intensity of effects and diminished control or regard for, or valuation of, the banal real world and its immediate requirements. I cannot, with any certainty, describe toxic doses in terms of temporal parameters (although these might be gleaned from sporadic reports).

Whether subthreshold doses in animals can produce any animal neurobehavioral component of the "loosening" of inhibition and inner-directed attention sought for by some clinicians in using less potent drugs for a kind of "psychosynthesis" is uncertain. Sensitization and habituation studies implicate raphe function but not in any simple way (32), and pavlovian studies show very low dose effects on sensory processing (39,43).

Route of administration may be an important variable to apply to animal research. Early fragmentarily reported investigations in humans indicate an onset after oral ingestion of early effects at about 30 to 40 min, with a more rapid onset with intramuscular injection, and even more rapid with intravenous injections; the latter, in my experience, when given slowly over a 2-min period, show an onset at around 20 min. As later noted, accelerating the rate of intravenous injection can bring on a brief, immediate effect. In two individuals receiving intrathecal injection, the onset noted by Paul Hoch (at Columbia University) was 1 to 2 min. The question is whether one can deduce something about the brain areas affected and perhaps specific receptors within the mass of different key brain areas that might be essential for the unique pattern of effects and the switching of attention from exterior to interior.

Thus it is clear, in both animals and man, that the clearance of drug is related to the period of acute effects, with plasma half-life values signaling their termination; for the human, this takes about five times as long as for the rat. The plasma half-life also signals a shift from the first phase of rat brain 5-HT, and 5-hydroxyindoleacetic acid (5-HIAA) changes [the point at which I have deduced that postsynaptic or feedback-induced inhibition of synthesis of 5-HT occurs (32–34); the presynaptic nerve ending signal for reducing tryptophan hydroxylase activity or blocking methiothepin stimulation of the enzyme occurs early in the course of events (9,42)]. The peak vesicular (or, after reserpine, juxtavesicular) retention of 5-HT occurs at this point (41,50,58), as drug appears to leave a particulate fraction (24,58) and be cleared from brain. In the rat, we know that brain concentrations of the drug peak within 1 or 2 min following intravenous injection (58); that gross behavioral effects of the drug (nose twitches, generalized piloerection, tachypnea, atactic hind limbs, periods of hypersensitivity to noise) occur sooner with the intravenous as compared to intraperitoneal route, and the duration of behavioral effects was somewhat shorter, correlating with slightly shorter half-life and shorter period of 5-HT-5-HIAA effects (58). We know, too, that plasma values are generally about 1,000-fold greater than brain values, and that clearance from different brain areas in which drug had been preferentially taken up closely follows the plasma half-life of LSD. We had some evidence (24) that there may be different clearance rates in a few regions, perhaps the anterior hippocampus being slightly slower. The role of the choroid is apparently important in drug clearance, with residual drug binding noted in autoradiography (18); the recent studies by Meibach et al. (55), elegantly demonstrating cellular aggregates and regional differences in the binding of drug, are interestingly discussed in terms of possible functional significance.

Thus there are regional and even subcellular aspects of the uptake and clearance of drug, with subsequent shifts in the regulation of 5-HT metabolism which may relate to function. In man, the period of drug clearance may be somehow accountable for the "march" of unfolding effects. In acute tolerance studies, one could observe events characteristic of the first 2 hr (i.e., the perception that something new was happening and perceptual illusions enhanced) when a second dose was given at 3 hr; the acute effects were briefer and the total duration of effects of doses so spaced was longer but not additive (26).

When the drug was given by rapid intravenous injection, rather than slowly over 1 or 2 min, subjects reported a different onset. Usually about 20 min after slow intravenous administration, there is a sudden and surprising shift in consciousness. This is described in terms of visual perception as a sudden awareness that what is at the periphery of the visual field is as important as that at the center; there are also odd feelings referred to the muscles or body, and occasionally slight dizziness and even nausea. Acute observers found, and others confirmed, an "oops, here we go" feeling in the pit of the stomach, or "like a roller coaster." One sees a facial flush most regularly, pupil size increasing, some perceptual illusory phenomena, and build-up of tension relieved by giggling. The initial shifts in attention may involve a sudden appreciation of the grain in wood, rather than the door itself; for several minutes, the change of state is what is impressive, with visual aspects and emotional lability gaining in intensity and frequency after the first hour and for the subsequent two. This may later be followed by laughing or crying in the second hour. At that time, there is an increasing absorption in internal feelings or in the distortion of objects in which adaptive perceptual behavior is diminished: aspects rather than the functions of objects dominate perceptual behavior. Elemental feelings—fear and exhilaration—coexist (26).

With rapid intravenous injection, it was as if the subsequent $3\frac{1}{2}$ hr were rehearsed as a preview of coming attractions. In brief, the intensity of visual illusions and quasihallucinatory experiences seemed initially to flick rapidly by for 2 or 3 min (as if they were clips of a movie); then the pace slows, and the initial effects (or adaptations to them) seemed to follow the usual sequence. Recalling that intensity and vividness of subjective effects in all its components—affective and visual—are characteristic of this enhancement of "highlights" with rapid injection, one wonders whether there are any leads or leverage with dose effects and rate parameters in determining critical sites of action. Pharmacodynamics in the human should account for the 20-min lag after slow intravenous injection; obviously, the onset can be pushed closer to time zero by controlling administration rate and route, but the unfolding of events appears related to clearance from brain tissues. Perhaps rapid access to tissue creates a brief dysequilibrium of drug content; but after equilibration, clearance of drug then regularly commences. Both events could produce "signals" of the characteristic drug effects. Animal study focused on these phenomena might clarify the issues.

Mydriasis and Phases of Drug Effects

A remarkable concomitant mydriasis appears to signal the triggering of the sequence of psychotomimetic effects. This is a dose-dependent response in both magnitude and duration of effect. Known to be centrally mediated, the neurobiologic study of this effect requires further scrutiny. Indeed, in studying the offset of effects—by asking when the human was no longer reacting to drug (the termination of the "second phase")—the time of the return of pupil size to normal seemed to reliably signal the subject's consensus (and retrospective consensus) as to the end of the trip. Mydriasis begins to decline at about 4 to 5 hr post-LSD, returning to normal at 8 to 10 hr after doses of 100 to 200 μg.

The course of post-LSD pupillary changes, with respect to dosage schedule and intensity and duration of effects, is a valuable tool. Pupil size 3 hr after the initial dose responded to the second dose of LSD and was an obvious measure to track in acute tolerance studies in humans. Given the number of rat studies in which this would be useful to monitor, the problem lies in determining rat mydriasis (easy in other animals); while a computerized pupillometer (developed by Martin Adler at Temple University) was informally tried by us once with LSD, systematic studies have not been done.

Mydriasis is also relevant to an underlying theme, that of "phases of effects." An overlooked effect in the human is important to note. In a study of chronically schizophrenic women (in whom typical LSD psychologic and behavioral effects, not an exacerbation of disorder, was noted), there was apparently a 24-hr effect: a matinal rebound increase in pupil size (21). Thus after the first dose, usual pupillary increases were noted (although I, unfortunately, do not recall precisely measuring the offset of effect in these subjects, pupil size had clearly begun to show the expected decrease at 4 to 5 hr). What was surprising was that if one measured pupil size 24 hr after each of three daily doses, the 9:00 a.m. pupil size was increased but showed tolerance with daily dosage. Tolerance during the first 6 hr after each dose was expectedly present (less mydriasis and shorter duration), but the 24-hr effect was unexpected. These women later received a large dose of reserpine; after 48 hr, when behavioral effects of reserpine had subsided, they were again studied with LSD for tolerance development. The subjects themselves had readily detected tolerance, and did so with LSD after the reserpine pretreatment; the usual mydriatic response to LSD and to the tolerance dosage regimen was also observed. When the 24-hr pupil size was examined, a different picture emerged. Reserpine alone had produced a matinal miosis which, in controlled studies, seemed to disappear after 7 days. After LSD, the matinal miosis was increased and did not show tolerance. We speculated that LSD might exhaust available stores of adrenergic mediators leading to an unmasking of the parasympathomimetic effects (too long ignored in LSD research), either of LSD or of reserpine, or of an effect of amine-depleted nerve endings on parasympathetic function. Since the effect of LSD at adequate time periods after reserpine-induced depletion is to enhance retention of 5-HT in a

juxtavesicular fraction in the nerve ending (32), and since we do not, to my knowledge, know the postreserpine effects of LSD on nerve ending catecholamines (as we do for indoleamines), there are obvious studies ahead. Further discussion of "compensatory" shifts at time periods after the initial dose is relevant to tolerance.

Tolerance

The third criterion that animal systems should demonstrate with respect to the psychedelic trip in man is the observed tolerance to both the mental effects and mydriasis. This appears to be complete after several daily doses and to be lost after 4 days without LSD. With respect to biologic mechanisms, occurrence of acute tolerance in both man and animals (20) poses a problem. Whether tachyphylactic or other processes are entailed remains to be defined.

In the rat, multiple low doses of LSD over days or weeks produce changes in 5-HT and NE turnover rates, but with measures taken many hours after the final dose (32–34). After a single dose, the initial changes (in the first 60 min where our behavioral and biochemical correlations have been focused) of nerve ending amine distribution are followed over the next 2 hr by longer lasting changes, such as the inhibition of conversion of 5-HT from labeled tryptophan and other indices of slowed turnover. This may be similar to the feedback inhibition induced by chlorimipramine (CMI) and its blockade of reuptake. With CMI, Halaris and I (32) saw an initial (30-min) increase of 5-HT (not in the juxtavesicular fraction) and decrease of 5-HIAA, followed for 2 hr by parallel decreases of 5-HT and 5-HIAA, congruent with 5HT-induced, postsynaptically mediated, or feedback inhibition. How the LSD sequence of changes are signaled requires investigation. Effects after a single dose in animals at time points throughout the 24-hr period following the initial LSD dose and similar time course studies after tolerance are needed. What is clear is that the effects during the first 60 min of LSD on brain tryptophan, 5-HT, and 5-HIAA [as well as brain tyrosine and dopamine (62) and plasma corticosterone (40)] show tolerance: there is an earlier termination of 5-HT effects and a diminished magnitude of 5-HIAA effects. Behaviorally, perhaps parasympathetically mediated effects, such as salivation and bradycardia, and other effects (diminished grooming) were noted as long as 90 min after injection (23). Biochemical correlates are not yet established, nor has tolerance been carefully studied for these effects.

In rats, we know that tolerance does not occur to parasympathomimetic effects of LSD at a time when sympathomimetically mediated and behavioral effects show tolerance. Apart from the postreserpine LSD-induced pupillary changes, such differential effects in man are not known. We know also that the bradycardia in unrestrained rats (19) converts readily to a tachycardia, and assertions that LSD elevates blood pressure or pulse in man should be viewed as reactivity rather than a direct effect.

With respect to the biochemical effects in animals and the behavioral effects

in man, tolerance is characterized not only by a decrement in specific effects but by a decreased intensity and magnitude and duration of effects. Thus by the third daily dose of LSD, the schizophrenic volunteers complained that they were not having the exciting effects of the first dose, and normal volunteers had noted that, even with the second dose, the "roller coaster effect" was regularly absent. There is, then, a shift to the left on any dose- or time-response curve with respect to tolerance and components of intensity that are blunted. How the initial "it's like adrenalin, but it isn't" (according to one experienced volunteer) effect is mediated is intriguing. How to determine the real basis for this, I cannot presently suggest. Fancifully, viewing the shift of all effects to the left, it is as if some initial effect occurs but is quickly compensated and some possible contingent subsequent effects are also diminished; i.e., there is a "minireaction" shortened in duration. If the phenomena were in any way linked to speeded up compensatory effects of 5-HT or NE systems (such as the increased 5-HT turnover 18 to 24 hr after multiple daily doses), animal studies over appropriate intervals will be needed. Furthermore, if 5-HT or catechol-mediated effects of LSD can influence the intensity of LSD effects, these may be obvious areas to pursue for characterizing the neurobiology underlying tolerance.

In our animal studies, it is apparent that one had to await the offset of the first 45 min of behavioral effects—perhaps 25 min more—before acute tolerance on rope climbing could be observed. If the second dose occurs during acute effects, there appears to be an enhancement of ongoing impairments. I speak only to the exquisite importance of temporal factors in producing a clear picture of tolerance. When these factors were appreciated, the long postponed demonstration of behavioral tolerance to dimethyltryptamine (DMT) in animals (49) was achieved. Half-life of drugs are somehow entailed; why, after short-acting drugs, the next dose must be sooner than 24 hr requires explanation.

Animal observations also point to a dimension of effects that have not been studied in humans. Thus in general, behaviors maintained by noxious reinforcement do not show tolerance; to my knowledge, this has not been searched for after daily doses in man. Nor has the cyclicity of tolerance with high dose been much investigated at either end of the bridge, although the waxing and waning of this phenomenon described by Koella et al. (48) points to some cyclic phenomena that must be occurring. In brief, there is evidence in humans that LSD induces a state in which aversive and competitive and conflictual stimuli are further disturbing, unpleasant, and indeed may contribute to post-LSD states where subjects are noted to avoid the noxious stimuli and strains of everyday life. Thus it would be important to study those behaviors that might be altered, even in the presence of what appears to be an organism tolerant to the psychotomimetic effects of LSD. Whether this would entail the use of evoked potential and information processing paradigms currently applied in the schizophrenias (15), or a study of adaptation to aversive stimuli, obvious research approaches are suggested. In our own observations in animals, it appears that, when tolerant, they are "willing to perform" rather than be distracted or absorbed by other stimuli during the acute phase of effects. When studying rat mounting

behavior in my laboratory, Gillette (37) noted a 40-min period of nonresponding which disappeared with tolerance, while the primary LSD effect of fewer "bucks for a bang" persisted. Rope climbing rats tolerant to LSD performed at the same speed but not with the same skilled movements. Thus the underlying sensitivities and deviations that may be uncovered during a tolerant state may help dissect components in both the LSD effects and mechanisms of tolerance.

Cross Tolerance

With appropriate dosage regimens, there is a cross tolerance of LSD and psychoactive congeners psilocybin, mescaline, and DMT. Although studies of tolerance development and loss with these substances have not been as systematically pursued as with LSD in humans, the phenomenon poses major questions as to which of the several different receptor systems, if any, under current study is uniquely relevant to that sequence of effects termed psychedelic. There is no cross tolerance to amphetamine. The series of methoxylated amphetamines developed by Shulgin have not been sufficiently described systematically in man for more than informed anecdote (57). The use of "mescaline units" to compare potencies (although not pattern of effect differences) appeared useful, but new human investigations are needed. There is no question that these substances, now used in currently select undergrounds, are relevant to this search and inquiry.

In general, in animal research, it is well to be cautious, whether bufotenin or 5-methoxylated tryptamines or other substances postulated to be useful "hallucinogenic" tools are used and to be aware of the status of knowledge of their effects in humans, let alone on a characteristic battery of effects in animals. In rat, for example, 5-methoxytryptamine (20 mg/kg) appeared to markedly increase 5-HT metabolism as judged by 5-HIAA, although interfering factors in measurement were not ruled out (29).

Obviously, it would be tempting to find those receptors or receptor-linked systems that provided some commonality (4,53), so that the effects of LSD and the spectrum of cross-tolerant drugs could be rationalized. The truly marked difference in biochemical effects (especially duration) and different aminergic mechanisms affected by these different but related psychotomimetics with respect to 5-HT and NE metabolism, and marked differences in duration of effects, have been emphasized elsewhere (33,34,63). How mescaline is and is not related to 5-HT calls for rigorous review and study. In summary, insofar as intensity of effects may be mediated by different characteristics of aminergic function, such factors should be sought in both man and animals in a more systematic way. The marked change in threshold dose for LSD after certain 5-HT depletions (of very small magnitude) is a key lead and paradigm for such studies.

Blockade, Attenuation, and Intensification

The question of blockade and modification or attenuation of the sequence of effects—of intensification or dampening of effects—requires precise and careful

definition. Unfortunately, with respect to BOL and blockade by chlorpromazine, the data in humans are not sufficiently precise to clarify issues for the animal researcher. While this is a topic for review in its own right, it is clear that BOL does not produce a typical psychedelic sequence in high dose, and the importance of distinguishing between subjectively fuzzy or hypnotic altered states and psychedelic effects is always important. It is evident that BOL does not produce the excitatory effects of LSD (in which plasma cortisol increases). It is most likely that a single dose does not block efficiently, and that BOL achieves clear-cut attenuating effects in man only when tolerance dosages are used preceding the LSD test. Why this would be so, on biologic grounds, is a puzzle.

Similarly, it is apparent that chlorpromazine does not prevent the LSD sequence of effects and, when given during the LSD experience, may mask perception of some of the changes but not the course of the march of events. Indeed, because of the effects of chlorpromazine per se, most clinicians treating "bad trips" have learned, if medications are to be used, to employ sedative antianxiety drugs, such as valium. Animal experiments tell us that remarkably small doses of chlorpromazine can be strikingly effective in blocking the effects of LSD on fixed ratio performance (30 μg/kg), and there was some early hint that less of a 5-HT elevation occurred with chlorpromazine pretreatment in rat brain (22).

In brief, LSD itself and pretreatment with psychoactive congeners are most effective in turning off or attenuating the LSD sequence of responses. Were human investigations possible today, systematic and rational design of pretreatment regimens could provide important tests of these issues and a variety of interesting hypotheses (e.g., possible effects of lithium, alpha-adrenergic agents, carbamazepine) designed to clarify mechanisms of action. Yohimbine, for example, while not psychedelic, produces a component seen to "oscillate" in LSD states (tension and anxiety).

Pretreatment with reserpine can enhance and prolong the LSD response in man (21). The paradigm used in our laboratories for both animals and man to study "drug-behavior interactions" was to conduct many tests after the acute effects of reserpine had diminished and most of the drug had been excreted (conceivably infinite amounts could be stored in membranes for the long period of reserpine effects). The effects observed 48 or 72 hr after reserpinization in humans were of a more intense LSD reaction with some degree of clouded consciousness and perhaps a prolongation of effects. On the other hand, when chronic MAO inhibition is established, the effects of LSD are diminished. The problem is to track in detail what components are diminished; but this order of information simply is not readily available. Therapists who have been using LSD clinically had also commented on this effect, but it is one that requires scrutiny so that useful detail is available to the animal researcher. Our own attempts to produce this in animals ran afoul of many complications in dosage regimens, but Lucki and Frazier (51) have indicated such an effect recently on the rat 5-HT "syndrome" and B. L. Jacobs (*personal communication*) in cats. Why it is that chronic MAO inhibition may be necessary (what is it that is

different in the chronically inhibited animal?) requires analysis; a panmonoaminergic subsensitivity of postsynaptic receptors might be investigated.

In attempts to deduce whether elevations of 5-HT would dampen LSD effects, agonistic effects of 5-hydroxytryptophan (5-HTP) have complicated animal studies. There are reports of mood changes and possibly some dampening effects on hallucinations in schizophrenic subjects with 5-HTP and, in one case, in a post-LSD psychosis (1). An agenda of human research as well as carefully conducted animal investigations is called for if we are to have precise definitions of blockade, attenuation, and intensification of effects. This is also relevant to the question of the magnitude of CNS changes necessary for the effects of a putative "psychotoxin" to be expressed. In animals, depletion of only 5 to 10% of 5-HT levels can lower the threshold dosage and intensify the effects of LSD (see refs. 32–34 for review). One is reminded of the small changes in 5-HT, produced by small doses of parachlorphenylalanine, that induce relapse of treated severe depressive disorders (39). The question of 5-HT antagonists blocking the hallucinogenic or psychotomimetic, rather than 5-HT-induced neuromuscular, effects or in drug detection paradigms requires focus. The search for a pure 5-HT antagonist recurrently promises a precise tool, and some progress is known. To apply these tools, at whatever receptor type they act, and to test for the range of biochemical, behavioral, physiologic, and electrophysiologic effects that have reliably characterized LSD and its interactions in animals (5) is necessary. In my view, the difficulties in demonstrating efficient blockade of LSD effects by 5-HT antagonists in such relevant paradigms are far more impressive than the successes. For specifically hallucinogenic and mental effects, such studies in man are lacking.

Dopamine Effects

Given the question of the interaction of LSD with CNS dopamine systems, there are tuberoinfundibular dopamine receptors for which LSD has high potency in man. Apart from this observation, with respect to biochemical, neurophysiologic, and behavioral responses to LSD, one does not see a dopamine agonist effect in animals without prior disruption or injury (such as axotomy or reserpine). In brain biochemical studies, it has been postulated that prior receptor occupancy may determine whether the usual antagonistic effects of LSD (e.g., signaling an increase of synthesis) occur. The only effect seen in humans that implicates dopamine was the occurrence of "antagonist" effects: oculogyric crises and extrapyramidal effects in some of the reserpine-pretreated women given LSD (21). In brief, we have no evidence of clear-cut dopamine-mediated mental effects of LSD, and the concept of prior occupancy might offer a research paradigm for human and behavioral studies.

Two "Psychotomimetic" Phases of LSD Effects

Human investigations point to dimensions for which psychobiologic study is relevant. I have noted the two phases of LSD effects relevant to understanding

the different "psychotomimetic" aspects of the LSD experience. Psychedelic experience in early phases of clinical psychosis (10), where meaningfulness and portentousness are prime characteristics of the experience (the sense of truth is enhanced, but not the necessity to test the truth of the senses), can occur in a variety of states where sensations and perceptions have heightened intensity and meaning. In studies of critical flicker fusion in pigeons (7), analysis of the effect of low dose LSD (20 μg/kg) in improving accuracy evoked the explanation of "enhanced sensory impact" of the flicker. This heightened awareness (differing from simple threshold effects) can be studied with sophisticated study designs.

Characterizing the psychobiology of the second phase in animals, of what in the human is clearly a paranoid state, also invites special research designs. The heightened vigilance and inefficient scanning (61) noted in humans to explain paranoid "mislocations" or misattributions (26) perhaps could provide a start. The EEG signs in animals of a shift in attentiveness and valuation of positive reinforcement (16,69,70), coupled with enhanced sensitivity to stimuli and noxious input, have also been noted (32). It should be remarked, however, that aspects of the first phase of the LSD experience—the heightened awareness, mislocation of cues, and the "visualness" or "sensoriness" of the experience—can be seen in a number of disorders. I have described this in watching the development of amphetamine psychosis, where, prior to interpretations and stabilizing delusions (which "explain" and "contain" what is odd), illusionary and heightened perceptual effects are quite common prodromes, and so too in the very early phases of delirium tremens. If amphetamine psychosis and the second phase of LSD are similar in man, differentiating these in animal study, and accounting for tolerance with one and not the other, provides an interesting challenge.

Perceptual Constancies and Distortions

This cannot be an occasion for scrutiny of the phenomenology of perceptual and hallucinatory changes induced by LSD. These have been reviewed in part by Siegel and Jarvik (60), and recent publications (2) focus on various aspects of the visual experience that may persist in chronic users. The characteristic persistence of reports of geometric frames against which perceptual illusions occur has long been noted, and a pioneer in such investigations, Heinrich Klüver (47), emphasized that aspects of the very mechanisms that process perception seem themselves to be brought into relief. As CNS visual systems are now elegantly characterized, further studies in animals seem possible. Klüver (47) noted the "anchoring" cortical systems to which information of the outside world arrives and the variability of subcortical systems; he speculated on hallucinogen-induced changes in the balances of these.

One could summarize many effects of LSD as affecting those stabilizing perceptual anticipations and adaptations, and those constancies and habits that normally smooth over the disparate details of our perceptions and actions. Thus

after one brief exposure, some individuals note persistent aftereffects. I reported (26) one of the first scientists working with LSD who was bothered for months after his single LSD experience by the flashing of the telephone poles at the periphery of his vision as he commuted daily, attempting to read his morning *London Times*. Normally, one can suppress the irrelevant in order to focus. There, in brief, is an apparent sensitization in which some aspects of the altered state can recur. Some individuals experience micropsias during the LSD state and do so in occasional flashbacks afterwards. The flashbacks do not appear to be like a television replay but do represent aspects of the experience that seem to persist and be reevoked, sometimes with external stress, sometimes without apparent explanation. How can a lifetime of perceptual habit be changed in a single, 6-hr experience? In those vulnerable to undesired long-term effects, the breakdown of constancies, whether these are viewed as perceptual or in terms of psychologic defenses (or in terms of regulation of the access of primitive thought and memories to consciousness), seems critical. This is clearly an important area for psychobiologic study.

One interesting aspect for study deriving from human investigation is the "double registration," the persistence of a mental image of what has just been seen, superimposed on an ongoing experience. For example, while I was measuring pupil size and asking individuals to look at a red X on the wall, one subject said to me: "You are Jesus Christ on the Cross." When queried as to why this florid expression of ambivalence toward a well-motivated researcher (with an odd middle name), he reflected that, in fact, he simply was able to see the X at the same time he was looking at me. This kind of overlapping—a failure to suppress a prior percept—was tested by Appel, Peterson, and myself in an uncompleted experiment in monkeys, where the animals were trained to respond differently to a circle and a square, and differently to the circle in a square. Under LSD, they frequently responded to the separated stimuli as if they were overlapping.

An interesting account of such perceptual changes, noted by a lifelong sufferer from Gilles de la Tourette's syndrome (8), suggests also that sensitization and subjective representation of sensorimotor processes (events occurring just prior to overt response) are dimensions requiring psychobiologic study in the "tic" syndrome. With Aghajanian's demonstration of facilitatory (but not direct) effects of both LSD and mescaline (iontophoretic or intravenous) on input to motor nuclei (53) [and, when given intravenously, on input to the locus ceruleus (4)], the feedback, if any, to sensory representations of this altered state of the motoneuron (or to "setting" sensory gates which seem strikingly "opened") would be of interest. One can wonder, when afferent flow to motor nuclei has enhanced effect, if there are also changes at the "upstairs" sources of input to these nuclei that might be subjectively registered. Thus Bliss (8) describes "mounting tensions" felt (or projected) on the skin and in muscle groups; for the compelling reduction of these tensions, action was needed. Prior to the tic, intense shifting phantom sensations, poorly confined as to modality (synes-

thesias?), were noted, along with the failure to confine a prior perceptual input to its normal temporal boundaries.

In this sense of altered sensorimotor processing, the pavlovian conditioning experiments with LSD and remarkable response to a very low dose of LSD in "sensory processing" is important to pursue with respect to neural processes entailed (39,43). In brief, LSD can be having effects on various different information processing aspects of stimulus and response, which may eventually provide a clue to some of these strange effects during the LSD experience, as well as aftereffects. Whatever the underlying mechanisms, they also could be relevant to the range of clinically encountered post-LSD phenomena.

POST-LSD EFFECTS

In terms of clinical disorders seen in a small subset of long-term users of LSD, studies are appearing with increasing frequency (11,12,14,66). Some (65) implicate a higher risk for "LSD psychosis," with strong family histories of major psychosis or psychopathology. Clinicians know that in these schizophrenia-like disorders with a history of drug use, there can be a ready precipitation of a period of acute symptoms triggered by continued drug use. Whether or not low cerebrospinal fluid (CSF) 5-HIAA proves to be a marker for vulnerability or is drug induced (11,14), it has been noted in these patients long after drug use is discontinued; acute changes in CSF are not yet studied, nor are total body measures of tryptophan metabolism available during the acute state in humans. The problem in these LSD-associated mental illnesses with a chronic course is that we do not know if LSD is a specific stressor in genetically vulnerable people, or whether in the very experience of LSD episodes there is a specific sensitization or learning or persisting biologic change that creates or reinforces vulnerability to subsequent psychotic states. Schizophrenic subjects are not more sensitive than others to the drug, nor did the group of postdelirium tremens subjects (picked for a history of three or more episodes) show a hallucinatory diathesis. Thus there is no ready explanation for these drug-associated disorders. The broad question is how LSD produces a short- or long-lasting change in the ability to regulate the switch between internal and external adaptations and between realistic and dereistic thinking and experiencing, which ranges from mild perceptual oddities to schizophreniform chronic psychoses.

Bowers and I (10,12) had characterized the LSD state as a multipotential state, out of which different outcomes, with respect to the particular trip, depended on prior expectancy and adaptations taking place within the drug state. The outcome could be seen as mystic, religious, a curiosity, a significant event, or a constant disturbance. I have indicated (26) that some of the LSD flashbacks were reminiscent of the traumatic war neuroses in which an unexpected experience (such as being buried alive by a shell burst) is repeatedly experienced as an intrusive and frightening memory, as if one were retrospectively trying to master an uncontrollable event. There is a psychobiology developing in which

the elicitation of behaviors to cope during a period of stress seems to lead to less noxious aftereffects; as such experimental paradigms advance, animal studies with LSD could be designed. While sensitization and habituation have been evoked in numerous LSD studies in man [and in studies of either the stimulation or ablation of the raphe nuclei (32)], one suspects that these complicated and probably different processes, along with facilitation, will be useful in understanding, at the neuronal level, these disorders of perception and sensitization to noxious inputs.

OVERALL TACTICS OR APPROACHES

Attempting to conceptualize these various disinhibitions, rearrangements, and enhancements of mental operations, I have argued (26,33) that LSD as a tool may be limited for a variety of reasons. One cannot have an LSD trip without the drug in sufficient quantity to affect an array of systems postsynaptic to the raphe, and probably other critically identified receptors. In other words, it is important to utilize LSD for what it can best explain and for the leads to basic processes it can provide. I have pointed to the heuristic utility of appreciating the small order of magnitude of biochemical change (5–10%) which could miscue and disrupt central signaling systems. If binding or carrier proteins or macromolecules within the nerve ending can be altered by LSD and the disposition of 5-HT thereby affected (32,41), at the least fundamental knowledge of basic processes from the regulation of 5-HT ion channels to a more refined grasp of processes regulating binding and release might ensue from such research, whatever its relevance to hallucinogenic events.

None of these leads can directly explain the psychedelic or hallucinogenic response; although it is clear that, among other neural systems, optic pathways are affected by LSD, various imbalances in other systems and in affect and cognition are involved. Furthermore, it is prudent to define each psychotomimetic drug in its own right. It is possible that LSD may have peculiar biophysical and biochemical effects not shared by psychoactive congeners, and we should not be surprised that slight molecular changes in any medicinal will produce not only a somewhat different range of effects but act through different mechanisms. Thus if there are different paths to the effects by which the compounds under question are commonly related, both commonalities and differences should be a key purpose guiding research in this area. Do the receptors linked to drug discrimination studies have any linkage to electrophysiologic or biochemical or other aspects of the LSD response? What processes account for cross tolerance of these different molecules with similar effects?

At the least, we should more systematically classify those drugs that produce a psychedelic sequence in man and show cross tolerance with LSD with respect to the different receptor systems that apparently rank order these drugs in terms of their potency. Such rank order effects have been noted on molluscan ganglia (35) in the clam heart on excitation of cardiac muscle; in liver fluke on glycolysis

and an adenylate cyclase system (52); directly on the cyclase in cockroach thoracic ganglia (57); on FR schedules of reinforcement (5); by Aghajanian on the most LSD sensitive of CNS tissues, the raphe perikarya; and on differences between raphe perikaryal and postsynaptic effects. These and other systems classify potency of LSD and related drugs fairly well; other systems do not. Without commenting on the question of what order of magnitude of effect in receptor binding studies (such as the S1 and S2 receptors) should be required, it would be helpful if some attempt at deducing physiologic ranges of the concentration of the involved amines and drugs were reported in *in vitro* studies. Low affinity binding sites have also been suggested as relevant (32). Similarly, the loose ascription of low and high dose across different species (without regard to half-life) or effector system need not continue to confuse discourse. ,

It would be useful to employ a standard array of drugs, of "R" and "S" isomers at equivalent dosages determined on reliable human and animal behavioral, physiologic, and receptor assays. Similarly, in utilizing agonists and especially serotonin antagonists, the pharmacology and physiologic effects of different agents should be mapped out to avoid false deductions of functional significance. The literature is replete with observations that require scrutiny or refutation [such as a putative hallucinogenic effect of the serotonin agonist, quipazine (70)]. Where synthesis or release is directly studied (45), this simplifies understanding of the aminergic effects of the different compounds; but where they are indirectly deduced, as generally is the case, confusion remains [such as that cited in a recent review (34) with respect to DOM and catechol turnover]. The above sampling is random, but the problem nevertheless is real.

Finally, the failure to utilize both threshold and maximal doses to determine correlations with a sequence and duration of effects, such as in electrophysiologic studies of postsynaptic events (32), may leave us in ignorance of similarities and differences among the psychotomimetics. I have also wondered whether the low potency of LSD (as compared to psychoactive congeners) in affecting NE release and synthesis (despite LSD enhancing input to the locus ceruleus) is at all related to the remarkable behavioral and biologic potency of the drug. The studies of Horita, fractionating excitatory and other effects of LSD in the rabbit and showing that after depletion, repletion with L-DOPA restores excitatory effects of LSD, still presents an unfinished story and one that, if pursued with other precursors and systems, might help in putting together the puzzling picture. Similarly, systematic study of the role of mescaline and phenylethylamines with respect to 5-HT receptors or 5-HT-mediated effects could clarify matters. Obviously, looking at the range of striking differences in regard to NE metabolism and duration of effects of drugs such as mescaline and psilocybin on NE (63) or on hydroxytryptamine (29), when compared to LSD, the question of their commonalities somewhere along the sequence of drug-induced CNS events remains a central challenge. Possible effects of psilocybin on reuptake and MAO (29) also require focus.

Electrophysiologic and behavioral observations in LSD-treated animals may give some hint as to the switch in attentiveness in the presence of a moderately high state of arousal, which is characteristic of LSD in man. One would expect further clarification of the physiologic role of the raphe with respect to REM sleep because, in nature, this is one state in which a natural shift to primary process thinking and plastic and sensory thought and perceptual processes (with a compelling sense of conviction) can occur.

The nervous system is constantly surprising because of the regulations that can occur in the absence of one or another key nucleus or amine (46). In general, however, it has been my impression that we seek eventually to reconstruct a picture of how the brain functions when its elements are present. Thus disruptions of one or another system have led us to appreciate the "unannounced" role of amines in modulating and buffering various sensory inputs and regulation of vital functions (23). In human investigations, one strategy has been to study those measurable aspects of arousal and evoked potentials found in schizophrenia, and to apply such measures to the animal or LSD-treated human (17); or we clinically look for a clue to altered receptors in brain in study of peripheral receptors. While we cannot tell from where we will derive essential new information, it should be possible to systematically compare the range of psychedelic compounds within the human, to use our knowledge of modern receptorology with respect to 5-HT and the catechols, to focus on key sensorimotor links or limbic and cortical "imbalances" in regulating sensorimotor functions, and to perceive, thereby, what is necessary and sufficient for the sequence of effects.

Whether techniques, such as PET, in animals or humans will advance our knowledge, the obvious gain will be in our ability to pose tougher questions. It is a difficult and elusive area in which to sort and seek the key mechanisms; what is astonishing is that, with each passing period of review, new and clarifying knowledge has ensued. This bridge watcher, while urging that we do intellectually and conceptually what we can to gain leverage on the problem, obviously believes that, with the current rate and direction of experiments, the bridge is well worth pacing.

REFERENCES

1. Abraham, H. D. (1983): L-5-Hydroxytryptophan for LSD-induced psychosis. *Am. J. Psychiatry,* 140:456–458.
2. Abraham, H. D. (1983): Visual phenomenology of the LSD flashback. *Arch. Gen. Psychiatry (in press).*
3. Aghajanian, G. K., and Freedman, D. X. (1968): Biochemical and morphological aspects of LSD pharmacology. In: *Psychopharmacology: A Review of Progress 1957–1967,* editor-in-chief, D. H. Efron, pp. 1185–1193. U. S. Government Printing Office, PHS Publication no. 1836, Washington, D. C.
4. Aghajanian, G. (1980): Mescaline and LSD facilitate the activation of locus coerulus neurons by peripheral stimuli. *Brain Res.,* 186:492–498.
5. Appel, J. B., and Freedman, D. X. (1965): The relative potencies of psychotomimetic drugs. *Life Sci.,* 4:2181–2186.

6. Barchas, J. D., and Freedman, D. X. (1963): Brain amines: Response to physiological stress. *Biochem. Pharmacol.*, 12:1225–1238.
7. Becker, D. I., Appel, J. B., and Freedman, D. X. (1967): Some effects of LSD on visual discrimination in pigeons. *Psychopharmacologia*, 11:354–364.
8. Bliss, J. (1980): Sensory experiences of Gilles de la Tourette syndrome. *Arch. Gen. Psychiatry*, 37:1343–1347.
9. Bourgoin, S., Artaud, F., Enjalbert, A., Hery, F., Glowinski, J., and Hamon, M. (1977): Acute changes in central serotonin metabolism induced by the blockade or stimulation of serotonergic receptors during ontogenesis in the rat. *J. Pharmacol. Exp. Ther.*, 202:519–531.
10. Bowers, M. B., and Freedman, D. X. (1966): Psychedelic experiences in acute psychoses. *Arch. Gen. Psychiatry*, 15:240–248.
11. Bowers, M. B., Jr. (1972): Acute psychosis induced by psychotomimetic drugs: I. Clinical findings. *Arch. Gen. Psychiatry*, 27:437–440.
12. Bowers, M. B., Jr., and Freedman, D. X. (1975): Psychoses associated with drug use. In: *American Handbook of Psychiatry, Vol. IV*, edited by M. F. Reiser, pp. 356–370. Basic Books, New York.
13. Bowers, M. B., Jr. (1975): Serotonin (5-HT) systems in psychotic states. *Psychopharmacol. Commun.*, 1:655–662.
14. Bowers, M. B., Jr. (1977): Psychoses precipitated by psychotomimetic drugs: A follow-up study. *Arch. Gen. Psychiatry*, 34:832–835.
15. Braff, L., Callaway, E., and Naylor, H. (1977): Very short term memory (VSTM) dysfunction in schizophrenia. *Arch. Gen. Psychiatry*, 34:25–30.
16. Brooks, D. C. (1975): The effect of LSD upon spontaneous PGO wave activity and REM sleep in the cat. *Neuropharmacology*, 14:837–857.
17. Claridge, G. (1978): Animal models of schizophrenia: The case of LSD-25. *Schizophr. Bull.*, 4:186–209.
18. Diab, I. M., Roth, L. J., and Freedman, D. X. (1971): ^{3}H Lysergic acid diethylamide: Cellular autoradiographic localization in rat brain. *Science*, 173:1022–1024.
19. Freedman, D. X., Aghajanian, G. K., Ornitz, E. M., and Rosner, B. S. (1958): Patterns of tolerance to lysergic acid diethylamide and mescaline in rats. *Science*, 127:1173–1174.
20. Freedman, D. X., and Aghajanian, G. K. (1959): Time parameters in acute tolerance, cross tolerance, and antagonism to psychotogens. *Fed. Proc.*, 18:390 (Abstr.).
21. Freedman, D. X. (1961): Studies of LSD-25 and serotonin in the brain. *Proc. 3rd World Cong. Psychiatry*, 1:653–658.
21a. Freedman, D. X. (1961): Effects of LSD-25 on brain serotonin. *J. Pharmacol. Exp. Ther.*, 134:160–166.
22. Freedman, D. X. (1963): Psychotomimetic drugs and brain biogenic amines. *Am. J. Psychiatry*, 119:843–850.
23. Freedman, D. X., and Giarman, N. J. (1963): Brain amines, electrical activity, and behavior. In: *EEG and Behavior*, edited by G. H. Glaser, pp. 198–243. Basic Books, New York.
24. Freedman, D. X., and Coquet, C. A. (1965): Regional and subcellular distribution of LSD and effects on 5-HT levels. *Pharmacologist*, 7:183 (Abstr.).
25. Freedman, D. X., and Aghajanian, G. K. (1966): Approaches to the pharmacology of LSD-25. *Lloydia*, 29:309–314.
26. Freedman, D. X. (1972): On the use and abuse of LSD. *Arch. Gen. Psychiatry*, 18:330–347.
27. Freedman, D. X. (1969): The psychopharmacology of hallucinogenic agents. *Annu. Rev. Med.*, 20:409–417.
28. Freedman, D. X. (1969): Research strategies with psychotomimetic drugs. In: *Psychochemical Research in Man*, edited by R. J. Mandell and M. P. Mandell, pp. 89–99. Academic Press, New York.
29. Freedman, D. X., Gottlieb, R., and Lovell, R. A. (1970): Psychotomimetic drugs and brain 5-hydroxytryptamine metabolism. *Biochem. Pharmacol.*, 19:1181–1188.
30. Freedman, D. X. (1970): Problems and prospects of research with hallucinogens. In: *Hallucinogenic Drug Research: Impact on Science and Society*, edited by J. R. Gamage and E. L. Zerkin, pp. 1–10. Stash Press, Beloit, Wisconsin.
31. Freedman, D. X. (1973): Psychotomimetic agents and our understanding of psychiatric disorders. In: *Textbook of Biological Psychiatry*, edited by J. Mendels, pp. 149–173. Wiley, New York.
32. Freedman, D. X., and Halaris, A. E. (1978): Monoamines and the biochemical mode of action of LSD at synapses. In: *Psychopharmacology: A Generation of Progress*, edited by M. A. Lipton, A. DiMascio, and K. F. Killam, pp. 347–359. Raven Press, New York.

33. Freedman, D. X. (1981): The mode of action of hallucinogenic drugs. In: *Handbook of Biological Psychiatry, Vol. II, Part IV,* edited by van Pragg, Rafaelsen, Lader, and Sachar, pp. 859–884. Marcel Dekker, New York.
34. Freedman, D. X., and Boggan, W. (1981): Biochemical pharmacology of psychotomimetics. In: *Handbook of Experimental Pharmacology, Vol. 55, Part III,* edited by F. Hoffmeister and G. Stille, pp. 57–88. Springer-Verlag, New York.
35. Gerschenfeld, H. M. (1971): Serotonin: Two different inhibitory actions on snail neurons. *Science,* 171:1252–1254.
36. Giarman, N. J., and Freedman, D. X. (1965): Biochemical aspects of the actions of psychotomimetic drugs. *Pharmacol. Rev.,* 17:1–25.
37. Gillett, E. (1960): Effects of chlorpromazine and d-lysergic acid diethylamide on sex behavior of male rats. *Proc. Soc. Exp. Biol.,* 103:392–394.
38. Gloor, P., Olivier, A., Quesney, L. F., Andermann, F., and Horowitz, S. (1982): The role of the limbic system in experiential phenomena of temporal lobe epilepsy. *Am. Neurol.,* 12:129–144.
39. Gormezano, I., Harvey, J. A., and Aycock, E. (1980): Sensory and associative effects of LSD on classical appetitive conditioning in the rabbit jaw movement response. *Psychopharmacology,* 70:137–143.
40. Halaris, A. E., Freedman, D. X., and Fang, V. S. (1975): Plasma corticoids and brain tryptophan after acute and tolerance dosage of LSD. *Life Sci.,* 17:1467–1472.
41. Halaris, A. E., and Freedman, D. X. (1977): Vesicular and juxtavesicular serotonin: Effects of lysergic acid diethylamide and reserpine. *J. Pharmacol. Exp. Ther.,* 203:575–586.
42. Hamon, M., Bourgoin, S., Hery, F., Ternaux, J. P., and Glowinski, J. (1976): In vivo and in vitro activation of soluble tryptophan hydroxylase from rat brainstem. *Nature,* 260:61–63.
43. Harvey, J. A., Gormezano, I., and Cool, V. A. (1982): Effects of d-lysergic acid diethylamide, d-2-bromo-lysergic acid diethylamide, d, l-2-5-dimethoxy-4-methylamphetamine and d-amphetamine on classical conditioning of the rabbit nictitating membrane response. *J. Pharmacol. Exp. Ther.,* 221:289–294.
44. Hawkins, R. D., Abrams, T. W., Carew, T. J., and Kandel, E. R. (1983): A cellular mechanism of classical conditioning in aplysia: Activity-dependent amplification of presynaptic facilitation. *Science,* 219:400–405.
45. Hery, E., Simonnet, G., Bourgoin, S., Soubrie, P., Artaud, F., Hamon, M., and Glowinski, J. (1979): Effect of nerve activity on the in vivo release of [^{3}H] serotonin continuously formed from L-[^{3}H]tryptophan in the caudate nucleus of the cat. *Brain Res.,* 169:317–334.
46. Jacobs, B. L., and Jones, B. E. (1978): The role of central monoamine and acetylcholine systems in sleep-wakefulness states: Mediation or modulation? In: *Cholinergic-Monoaminergic Interactions in the Brain,* edited by L. Butcher, pp. 271–290. Academic Press, New York.
47. Klüver, H. (1966): *Mescal and Mechanisms of Hallucinations.* University of Chicago Press, Chicago.
48. Koella, W. P., Beaulier, R. F., and Bergen, J. R. (1964): Stereotyped behavior cyclic changes in response produced by LSD in goats. *Int. J. Neuropharmacol.,* 3:397–403.
49. Kovacic, B., and Domino, E. F. (1976): Tolerance and limited cross-tolerance to the effects of N,N-dimethyltryptamine (DMT) and lysergic acid diethylamide-25 (LSD) on food-rewarded bar pressing in the rat. *J. Pharmacol. Exp. Ther.,* 197:495–502.
50. Lovell, R. A., Rosecrans, J. A., and Freedman, D. X. (1967): Effects of LSD on rat brain serotonin metabolism. *Fed. Proc.,* 26: no. 2. (Abstr.).
51. Lucki, I., and Frazer, A. (1982): Prevention of the serotonin syndrome in rats by repeated administration of monoamine oxidase inhibitors but not tricyclic antidepressants. *Psychopharmacology,* 77:205–211.
52. Mansour, T. E., Sutherland, E. W., Rall, T. W., and Bueding, E. (1960): The effect of serotonin (5-hydroxytryptamine) on the formation of adenosine 3′,5′-phosphate by tissue particles from the liver fluke, Fasciola hepatica. *J. Biol. Chem.,* 235:466–470.
53. McCall, R., and Aghajanian, G. (1980): Hallucinogens potentiate responses to serotonin and norepinephrine in the facial motor muscles. *Life Sci.,* 26:1149–1156.
54. McGlothlin, W. H., Arnold, D. O., and Freedman, D. X. (1969): Organicity measures following repeated LSD ingestion. *Arch. Gen. Psychiatry,* 21:705–709.
55. Meibach, R. C., Maayani, S., and Green, J. P. (1980): Characterization and radio-autography of [^{3}H] LSD binding by rat brain slices in vitro: The effect of 5-hydroxytryptamine. *Eur. J. Pharmacol.,* 67:371–382.

56. Nathanson, J. A., and Greengard, P. (1974): Serotonin-sensitive adenylate cyclase in neural tissue and its similarity to the serotonin receptor: A possible site of action of lysergic acid diethylamide. *Proc. Natl. Acad. Sci. USA,* 71:797–801.
57. Naranjo, C. (1973): *The Healing Journey.* Pantheon Books, New York.
58. Rosecrans, J. A., Lovell, R. A., and Freedman, D. X. (1967): Effects of lysergic acid diethylamide on the metabolism of brain 5-hydroxytryptamine. *Biochem. Pharmacol.,* 16:2011–2021.
59. Shopsin, B., Friedman, E., and Gershon, S. (1976): Parachlorophenylalanine reversal of tranylcypromine in depressed patients. *Arch. Gen. Psychiatry,* 33:1051–1058.
60. Siegel, R. K., and Jarvik, M. E. (1975): Drug-induced hallucinations in animals and man. In: *Hallucinations: Behavior, Experience, and Theory,* edited by R. K. Siegel and L. J. West, pp. 81–162. Wiley, New York.
61. Silverman, J. (1967): Variations of cognitive control and psychophysiological defense in the schizophrenias. *Psychosom. Med.,* 29:225–251.
62. Smith, R. C., Boggan, W. O., and Freedman, D. X. (1975): Effects of single and multiple dose LSD on endogenous levels of brain tyrosine and catecholamines. *Psychopharmacologia,* 42:271–276.
63. Stolk, J. M., Barchas, J. D., Goldstein, M., Boggan, W. O., and Freedman, D. X. (1974): A comparison of psychotomimetic drug effects on rat brain norepinephrine metabolism. *J. Pharmacol. Exp. Ther.,* 189:42–50.
64. Trulson, M. E., and Jacobs, B. L. (1977): Usefulness of an animal behavior model in studying the duration of action of LSD and the onset and duration of tolerance to LSD in the cat. *Brain Res.,* 132:315–326.
65. Tsuang, M. T., Simpson, J. C., and Kronfol, Z. (1982): Subtypes of drug abuse with psychosis. *Arch. Gen. Psychiatry,* 39:141–147.
66. Vardy, M. M., and Kay, S. R. (1983): LSD psychosis or LSD-induced schizophrenia? A multimethod inquiry. *Arch. Gen. Psychiatry (in press).*
67. White, F. J., and Appel, J. B. (1982): Lysergic acid diethylamide (LSD) and lisuride: Differentiation of their neuropharmacological actions. *Science,* 216:535–537.
68. Wiener, H. (1967): External chemical messengers: III. Mind and body in schizophrenia. *NY J. Med.,* 67:1287.
69. Winters, W., and Wallach, M. (1970): Drug induced states of CNS excitation: A theory of hallucinosis. In: *Psychotomimetic Drugs,* edited by D. H. Efron, pp. 193–214. Raven Press, New York.
70. Winters, W. D., Alcaraz, M., Cervantes, M. Y., and Guzman-Flores, C. (1973): The synergistic effect of reduced visual input on ketamine action: The possible role of the pineal gland. *Neuropharmacology,* 12:407–416.
71. Winters, W. D. (1975): The continuum of CNS excitatory states and hallucinosis. In: *Hallucinations: Behavior, Experience, and Theory,* edited by R. K. Siegel and L. J. West, pp. 53–70. Wiley, New York.